IN THE SPECIFICATION

On Page 1, second paragraph under the heading "Background of the Invention", lines 30-43 through page 2, lines 1-37 (as numbered), replace with:

~~--The vectors used in gene therapy solely have not curative potential =. On the other hand, the genes which could be used to treat the diseases only have potential treating capability, since it is very difficult for them to directly enter and then express in the target cells. In order for the potential therapeutic genes to take effect, the vector should first be recombined with the gene, then carry the gene into the target cells by transfection, and finally the gene could enter the cells and be expressed. Therefore, the key of gene therapy is to construct the recombinant DNA for the therapeutic gene and the gene vector.~~

~~The common way to recombine the target gene expression cassette with its vector is to carry out homologous recombination in eukaryotic cells, which is a very complicated and tedious process. However, using prokaryotic cells for homologous recombination and to construct recombinant vectors could solve the above problems.~~

~~A bottleneck in gene therapy lies in the lack of specific, targeting and efficient gene vectors. At present, there are two kinds of vectors used in gene therapy research including viral vectors and non-viral vectors. The common viral vectors include adenovirus vectors, adeno-associated virus vectors and retrovirus vectors. Adenovirus vector is the most common. Its advantages include a high transfection rate, its relative safety and ease of operability, the ability to carry large gene fragments and the ability to prepare high titer viral particles, suitable for production, and the ability to infect cells not only in division phase but also in non-division phase. However, its disadvantages include a lack of target-specific infection and production of immunogenicity. Therefore, it is necessary to improve adenovirus vector for gene therapy. Research indicates that a gene carried by adenovirus vector could be expressed in a longer period time and the antigenicity of the vector could be decreased if the gene is carried at E1 or E3 missing area. The retrovirus vector could carry a foreign gene and integrate into the target cell's genome, thus realizing the stable and lasting gene expressions. However, the retrovirus has the following disadvantages: low reproduction titer *in vitro*, low transfection efficiency, infecting only the cells in division phase, and random recombination with chromosomes bringing potentially carcinogenic activity. Other viral or non-viral vectors used in gene transformations all have different advantages and disadvantages.~~

~~**Summary of Invention**~~

~~The object of this invention is to recombine the potentially therapeutic genes with their vectors, thus providing a recombinant DNA of adenoviral vector and p53 gene for treatment of hyperplasia. This recombinant product will then induce the hyperplastic cells express~~

~~normal P53 proteins. In this way the proliferation of the abnormal cells could be effectively repressed and could be used to treat hyperplastic diseases such as cheloid.~~

~~The object of this invention is also to provide a method for producing this recombination and its preparation so that it could be put in practices.~~

~~This invention provides recombinant DNA of adneoviral vector and p53 gene. This recombination is constructed by combining adenoviral vector and human tumor suppressor gene expression cassette, which has the following sequence:~~ The common medicines for proliferative disease are (1) corticosteroid, which is effect to small pathological scar, but could induce local skin shrink, pigment decrease or decolor, telangiectasis, even skin necrosis and elkosis. It will seriously cause general reaction, such as hypertension, osteoporosis, digestive tresis, teratocarcinoma, even Cushing's response; (2) tretinoin, which is seldom used for treating scar; (3) tranilast, which need to administrate for more than 6 months. Surgical treatment, laser treatment, radiation treatment and compression method also can be used for treating proliferative disease.

In the developing of the study of the relative genes in pathological scar, some controlling genes of fibroblast cells propagation-apoptosis and metabolism of collagen have been cloned and described. Therefore, gene therapy for proliferative disease appears.

The present applicant discloses a recombinant, which can amplify and propagate in specific genetic-engineered cell lines, and also can express tumor suppressor protein in eukaryote cells. The recombinant vector can be either DNA virus or RNA virus. The preferred vector is adenovirus vector or combined vector containing adenovirus vector sequence. The most preferable vector is the adenovirus vector.

The human tumor suppressor gene can be any tumor suppressor genes, the most preferable one is p53.

The recombinant combined with adenovirus vector and p53 gene is defined as recombinant p53 adenovirus, which has the following sequence:--

On page 4, lines 10-21 (as numbered), replace with:

--In which:

1. the right end of adenovirus 5 and the left end of adenovirus 5end are described in adenovirus 5 gene full sequence (Genbank No: NC_001406)
2. 1-70: the right arm of adenovirus (the 70th base locates at adenovirus gene sequence 3328)

3. 71-523 : Rous Sarcoma Virus (RSV) LTR (promoter)
4. 524-655: 5' end non-translating region
5. 656-1837: p53 gene coding sequence
6. 1838-2733: 3' end non-translating region (poly Adenosine tail starting at 2298)
7. 2734-2848: the left arm of adenovirus (base at 2734 is positioned at 452 of adenovirus 5 gene sequence).--

On page 4, please delete lines 38-39 of the specification.

On page 6, lines 9-13, second paragraph, replace with:

--2. Application: This recombinant ~~medicine not only could be used to treat many malignant tumors, but also could be used to treat many proliferative diseases. It~~ p53 adenovirus was a broad spectrum anti-tumor medicine. It could be used to treat many malignant tumors. The phase II clinical trials indicated that it had significant treatment effects on head and neck squamous carcinomas and lung cancer, among others. The recombinant p53 adenovirus was especially effective in preventing tumor recurrence. The phase I clinical trial and 3 years post-surgery observations indicated that this recombinant p53 adenovirus had prevented the post-surgery relapse of the larynx cancer patients as a cancer vaccine.

The recombinant p53 adenovirus of this invention could be made into medicines for treatment of many malignant tumors in the experiement. And it could be made into medicines for prevention of tumorigenesis and post-surgery relapses of tumors.

The present applicant also found the recombinant p53 adenovirus could induce the abnormal hyperplastic cells expressing normal P53 protein, thus effectively repressing the cell reproduction and curing hyperplastic diseases including cheloid.--

On page 6, before line 14, please insert:

Summary of the Invention

The object of this invention is to recombine the potentially therapeutic genes with their vectors, thus providing a recombinant DNA of adenoviral vector and p53 gene for treatment of hyperplasia. This recombinant product will then induce the hyperplastic cells express normal P53 proteins. In this way the proliferation of the abnormal cells could be effectively repressed and could be used to treat hyperplastic diseases such as cheloid.

On page 7, lines 10-38, under the heading "Detailed Description of the Figures", replace with:

--Figure 2 is the flow chart of the experimental protocols for the production of the recombinant medicine.

Figure 3 is the stability testing diagram of agarose gel electrophoresis of the recombinant gene after generations of passage, which was made by PCR to amplify the recombinant p53 adenovirus using 5′ CCACGACGGTGACACGCTTC and 5′ CAAGCAAGGGTTCAAAGAC as primer, and p53cDNA as template. PCR amplification of the recombinant p53 adenovirus obtains a 1400bp DNA fragment.

1. DNA marker ; 2, 3, 4 The PCR results of the p53 cDNA.

Figure 4 is the result analysis diagram of agarose gel electrophoresis of the PCR amplification of virus DNA, which was obtained 36 hours after cell 293 was infected by recombinant gene (preserved by SiBiono Corp., preservation No.: No-1, same as the following). The DNA fragment is 2750 bp.

1. DNA marker ; 2. The PCR results of the recombinant p53 adenovirus.

Figure 5 is the Western blot analysis result 36 hours after the Hep-2 and H1299 cellswere infected by recombinant adenovirus. The expression of p53 carried by the recombinant p53 adenovirus in Hep-2 cells and H1299 cells.

1. Protein marker; 2-3. Negative controls: Hep-2 cells and H1299 cells without infecting bySBN-1, respectively; 4-5. Hep-2 cells and H1299 cells infecting bySBN-1, respectively.

Figure 6 is the primary cultured fibroblasts of human hypertrophic scar *in vitro*. The continuous fibroblasts are in order, exhibit nodular or helix form. The fibroblasts are spindle or irregularity, and the cell boundary is clear under the optical microscope.

Figure 7 is the characterization of the fibroblast cells using S-P staining and vacuum. The cytolymph of the c cells using S-P staining and vacuum is brown, and the nucleuses are blue. All the continuous cells are fibroblasts and can produce protocollagen III because they are position cells.

Figure 8 is the microscopic photo of the killing effect of the recombinant gene to the scar fibroblast cells *in vitro*. B, C, D counts the configuration changes of the Scar fibroblast cells, which are infected with recombinant adenovirus after 24h, 48h, and 72h. The volume of the cells is increase, and change from spindle to polygonal, the cytolymph is also increase, and the nuclear division is decrease and appears dissociation and avalanche. However, the configuration of the control cells is not change significantly.

Figure 9 is the electron micrograph of the killing effect of the recombinant gene to the scar fibroblast cells *in vitro*. The observation (Fig. 9A, B, C) under transmission electron microscope exhibits the process of bubbling, appearing apoptotic body, and the apoptotic body casting in the cells with the recombinant medicine (MOI=200). Fig. 9D expresses another situation of apoptosis, which is the obvious increasing of chondriosomes.

Figure 10 includes the pictures of the effect of recombinant gene to the cheloid patient before and after treatment. The size of the scar had significantly decreased after gene therapy for 4 weeks.--